International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 546-556 www.ijprajournal.com ISSN: 2249-7781

Synthesis, Drug Design Studies,and Biological Evaluation Studies Of Nickel Based Schiff Bases

Patel AP*, Dudani TD, Dwivedi ND, Patel SP
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Shri Ram Group of Institutions, Jabalpur, Madhya Pradesh, India

Date of Submission: 15-09-2021 Date of Acceptance: 28-09-2021

ABSTRACT

Introduction: Heterocyclic Schiff base metal complexes attract more attention in biological application and also show interesting co-ordination chemistry.In this article the various fields where the Schiff base complexes finds applications and several aspects explored by the researchers has been reviewed in detail.**Material and method:** In this research article a novel Schiff base transition metal complexes of Ni(II) have been design and synthesized by reacting metal salts of nickel. All newly synthesized metal complexes were characterized by spectroscopic data and screened for UV, Visible, infrared and FTIR spectra.**Conclusion:**The antimicrobialresults obtained reflected that the ligand exhibited a good activity. Schiff bases and some of their complexes were found to be highly active against some of the fungi species. Also inhibition by metal complexes was higher than that of the free ligands and corresponding metal salts against the same bacterial organisms under identical experimental conditions.Also the biostatistical data of antimicrobial and anti-oxidant activities of synthesized metal complexes indicates moderate to good results.

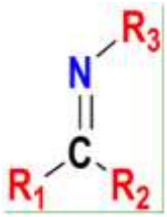
I. INTRODUCTION

Schiff bases are versatile ligands having imine or azomethine (–C=N–) functional group, first described by Hugo Schiff, German Chemist in1864 and hence they are named so. Schiff bases are the backbone of large number of organic compounds and have enormous applications in many fields including
-analytical,
-biological, and
-inorganic chemistry.

Schiff bases are well known for their wide range of applications and are useful intermediates in organic synthesis. These compounds have intrinsic biological activities including anticancer, anti-inflammatory, antitubercular, antioxidant, antibacterial, analgesic, antifungal and antifertility, herbicidal, anticonvulsant, anthelmintic and antiproliferative. Moreover, Schiff bases also exhibit fluorescence, photoluminescence, a potentiometric cation caring and aggregation properties.

Structure and properties of Schiff base

The functional group of Schiff base contain a carbon-nitrogen double bond with nitrogen atom connected to an alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted, other than with hydrogen. Scheme 1 shows the general formula of azomethine group which is the most common structural feature of Schiff [(1)].



Scheme 1. General formula of Schiff base having azomethine linkage(R is an organic side chain)

Schiff bases are weak bases and are easily hydrolyzed by dilute mineral acids, but not by aqueous alkali. They also form insoluble salts with strong acids through coordination of the electrons on nitrogen atom of azomethine group.[(2)] Most of the Schiff bases are stable in alkaline solutions. Aromatic aldehydes especially with an effective conjugation system, form stable Schiff bases,

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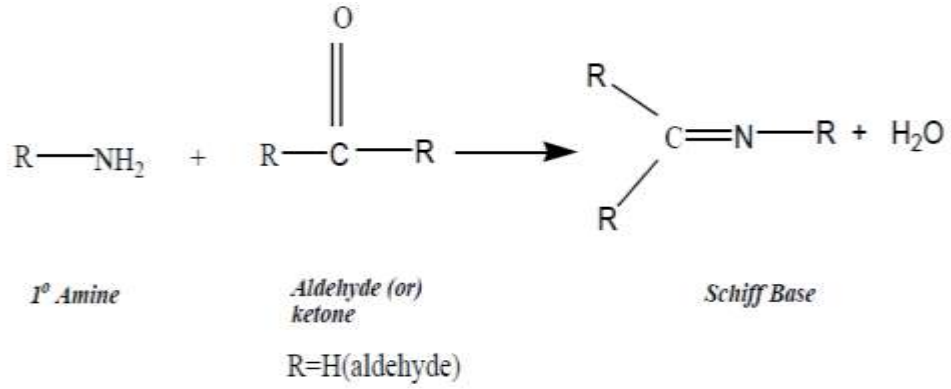
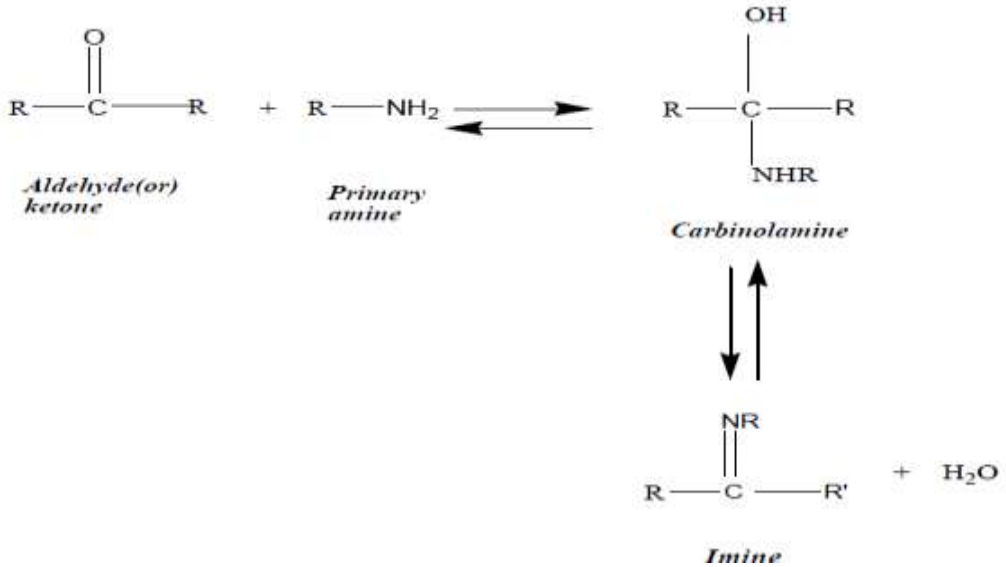
where as those from aliphatic aldehydes are found to be less stable. Aliphatic Schiff bases have a tendency to polymerize and are difficult to isolate . Aldehydes can form Schiff base ligands more readily than ketones. This is because the reaction centers of aldehydes are sterically less hindered than ketones and the additional carbon of ketone contributes more electron density to the azomethine carbon making them less electrophilic compared to aldehydes .[3,4]

Reaction involved



Mechanism

The formation of a Schiff base from an aldehydes (or) ketones is a reversible reaction and generally takes place under acid (or) base catalysis, or upon heating.[5] The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.



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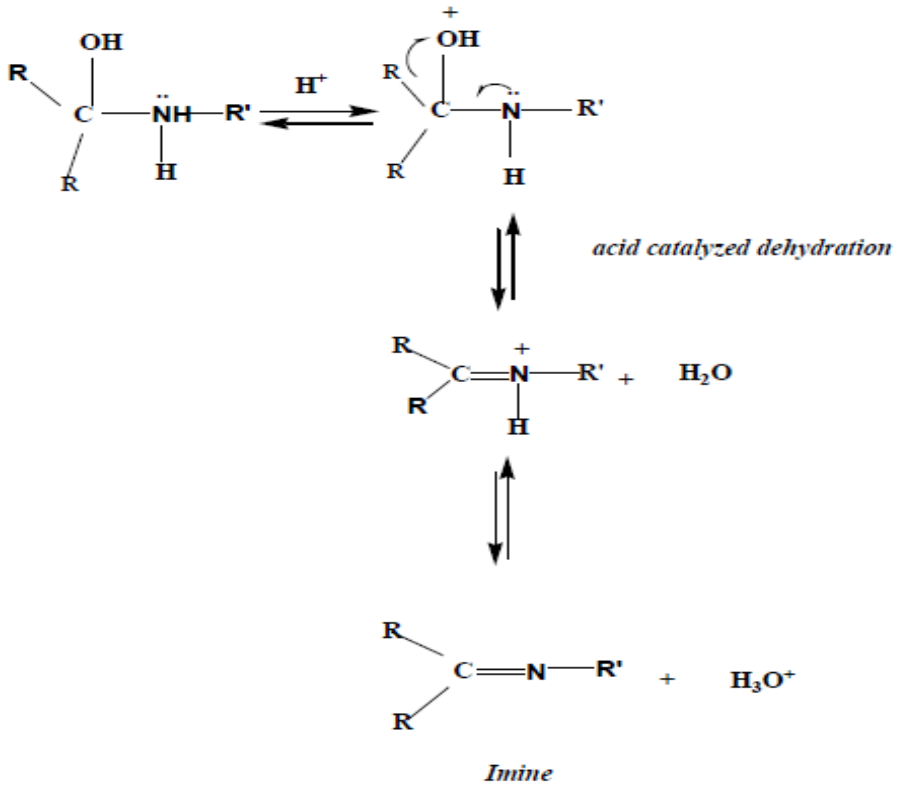

Imine

The dehydration of carbinolamine is also catalyzed by base. This reaction is somewhat analogous to the E2 elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate.

The Schiff base formation is really a sequence of two types of reactions, i.e**. addition** followed by **elimination.**

Importance of heterocyclic Schiff's base transition metal complexes

Schiff bases derived from heterocyclic scaffolds mainly sulfur, nitrogen and oxygen atom have great significance in many areas like biological, clinical, medicinal, analytical and pharmacological field.[6] Schiff base transition metal complexes obtained from heterocyclic molecules have been known to possess a wide range of biological and pharmacological activities. In recent years, they have received significant interest from many researchers in the area of drug research and development owing to their broad bioactivities such as antibacterial, antifungal, anti-inflammatory, anticonvulsant, antiviral and anticancer activities. Heterocyclic Schiff-base metal complexes are considered to be among the most important stereochemical models in main group and transition metal coordination chemistry due to their ease of preparation and structural variety.[7,8]

Applications of Schiff base and their transition metal complexes

Schiff bases are used as starting material in the synthesis of industrial and biological compounds such as lactams, used in the construction of poly vinyl chloride powder (PVC) based membrane selective sensors and also as ionophore in metal ion-selective electrodes. Schiff base ligands are able to coordinate many metals and to stabilize them in different oxidation states.[9] Multidentate Schiff bases ligands have been widely used, as they can form highly stable coordination compounds on coordination with metal ions. Schiff base transition metal complexes exhibit well-defined coordination geometries and are attractive moieties for reversible recognition of nucleic acids research.Schiff bases have been used in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, via ring closure, cyclo addition, and replacement reactions .[10]

The catalytic activity of metal complexes has been reported in various reactions as given below.

- Polymerization reaction

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- Reduction of thionyl chloride
- Oxidation of organic compounds
- Reduction reaction of ketones
- Aldol reaction
- Epoxidation of alkenes
- Henry reaction

II. MATERIALS AND METHODS

Material method

The synthesis of Schiffbase ligands of amino acids (Glycine, Phenylalanine and Tyrosine) with salicylaldehyde and their mixed ligand ternary Cu(II) complexes are discussed. Other ligands are used in co-ordination with the schiff base is 1,10-Phenanthroline/thiourea in equimolar ratio. The environmentally efficient and modern developed method for synthesis is the solid state synthesis of salicylidene amino acids through pestle mortar synthetic procedure. All chemical compounds used throughout the work are of merckmillipore origin. They are supplied as methanol, sodium hydroxide, glycine, and benzaldehyde and purified with an analytical grade.(11)

Physical measurement

Quantitative structure–activity relationship (QSAR) methodology was applied to explore the correlation between antibacterial activity and compound structures. The two best QSAR models showed R2 = 0.9354, F = 57.96, and s2 = 0.0020 against Escherichia coli, and R2 = 0.8946, F = 33.94, and s2 = 0.0043 against Staphylococcus aureus. The complexes are characterized by spectral techniques IR spectroscopy and UV spectroscopy.(12) The investigations concluded that the pestle mortar assisted method is very rapid , simple and economic for the preparation of ligands and complexes as well. The azomethine bonding(-CH=N-) between salicylaldehyde amino acids based Schiff bases is described by the IR spectral peak around 1600 cm-1.**Sharma et. al., Vol.4 (Iss.12: SE): December, 2017]**

Instrumental

The MP's of solid Schiff bases and nickel complex are measured by electrothermal m.p apparatus model BÜCHI 510.

The IR spectra for solids Schiff bases and Nickel complex are measured by a computerized FTIR, Thermo Fischer model Nicolet iS5.(13)

The UV for 1mg/ml DMSO/methanol (1:1) solutions of Schiff bases and nickel complex are measured by a double beam ThermoFischer type model Aquamate 8000. Quartz cells of dimensions 1×1×3 cm^3 are used.

BIOLOGICAL EVALUATION -

Evaluation of antibacterial activity

- **Procedure**

The in vitro biological screening effects of the investigated compounds were tested against the bacteria: Bacillus subtilis, E.coli and Klebsiella pneumonia was carried out by the agar well diffusion technique, using agar nutrient as the medium (Arora et al., 2011). The stock solution (1mg/ml) of new compounds was prepared by dissolving the compounds in DMSO and methanol(1:1). In a typical procedure, a well was made on the agar medium inoculated with microorganisms. The well was filled with the test solution using a micropipette and the plate was incubated for 24 h at 37 LC.

All thionine Ln (III) complexes and the Schiff base ligand was studied against Pseudomonas aeruginosa, Klebsiella and Escherichia coli bacteria.(14)

- **Result**

During this period, the test solution diffused and the growth of the inoculated microorganisms was affected. The results were recorded by measuring the growth inhibition surrounding the disk.The in vitro antibacterial activity against bacteria such as Staphylococcus aureus and Escherichia coli, by paper disc plate method, show that the inhibition by metal complexes was higher than that of the free ligands and corresponding metal salts against the same organism under identical experimental conditions.

It was observed from the result that most of the synthesized complexes of the tested series possessed good antibacterial activity against bacteria and the microbial activity of the complexes in most cases is higher than that of the corresponding ligand.

The nickel(II) complex exhibited the maximum antibacterial activity against all organisms used in this study and recorded high inhibition activity against klebsiella pneumonia comparable with standard drug. Moreover, ligand showed moderate activity against S. aureus microorganism comparable with ligand and standard drug ampicillin, while against P. aeruginosa the results do not record any biological activity of this complex in both concentrations (fig).

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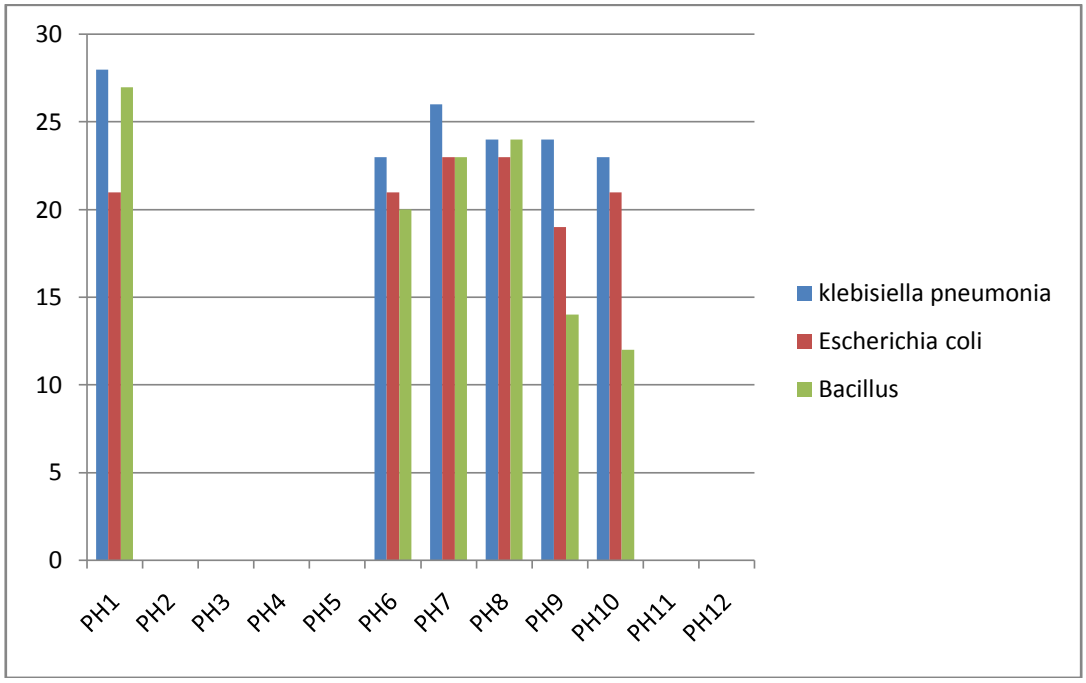
S.NO	Compounds	Klebsiella pneumonia	Escherichia coli	Bacillus
PH1	Ampicillin	28.00	21.00	27.00
PH2	DMSO	NIL	NIL	NIL
PH3	DMSO	NIL	NIL	NIL
PH4	DMSO	NIL	NIL	NIL
PH5	SB ligand	NIL	NIL	NIL
PH6	Ampicillin	23.00	21.00	20.00
PH7	Ni	26.00	23.00	23.00
PH8	Ni	24.00	23.00	24.00
PH9	Ni	24.00	19.00	14.00
PH10	Ampicillin	23.00	21.00	12.00
PH11	SB ligand	Nil	Nil	NIL
PH12	SB ligand	Nil	Nil	NIL



Evaluation of antimicrobial activity

- **Procedure**

Biological and pharmaceutical activities of Schiff base derived from 2-thiophene carboxaldehyde and aminobenzoic acid have been studied in comparison to Cu, Fe, Zn, Ni and Co complexes by Safaa et al (2011) [65]. These compounds were screened for the antimicrobial activity against bacterial species and fungal species.

Schiff base ligand bis-(salicyladehyde)-1,3-propylenediimine was screened for the antibacterial activity.[15]

- **Result**

E. coli was inhibited by Fe, Cu and Zn complexes and Candida species was inhibited with low inhibition zone.

The results obtained reflected that the ligand exhibited a good activity against Pseudomonas aeruginosa and Shigella dysenteriaeand do not show any activity against Proteusvulgaris.

Ln (III) complexes possessed a high antibacterial activity against the Gram-negative bacteria tested.

Evaluation of antifungal activity

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Schiff bases and some of their complexes were found to be highly active against Aspergillus niger, Aspergillus flavus and Cladosporium fungi.[16]

Evaluation of anti-oxidant activity

- **Procedure**

Schiff base ligand and its lanthanide complexes, [Ln(H2L)(NO3)2 . 2H2O]NO3, ((Ln = La, Pr, Nd, Sm, Eu, Gd, Tb, Dy and Er) (H2L = Schiff base ligand)) was determined by its scavenging ability on the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical.[17]

- **Result**

Ln (III) complexes are significantly more efficient in quenching DPPH radical than the free ligand. The metal complexes showed better antioxidant activities than the ligand.

Synthesis of Schiff bases

The general theoretical procedure of synthesis is by mixing 10^{-2} mole each of benzaldehyde with the suitable
amino acid and sodium hydroxide in ethanol,[18] as in the following details:-

Synthesis of benzylidene glycine-

In 50 ml round bottom flask attached with a reflux condenser, mix 1.06 g of benzaldehyde, (0.75g) of glycine or (0.89g) of and (0.4g) of sodium hydroxide. Add 20 ml of ethanol to each mixture and the final mixture is refluxed for 3 hours for benzylidene glycine . The mixture is cooled and filtered. Products are washed with cold ethanol and dried. Pure products have a melting points of 195C° (decomp.) and 110C° for Schiff bases.

Synthesis of complexes

A general method has been used for the preparation of the new complexes by the reaction of the hydrate metal salts nickel which dissolved in 5 ml of absolute ethanol and 0.378 g, 1 m mol of the Schiff base ligand at a metal to ligand molar ratio of 1:1, while 0.756 g, 2 m mol at a metal to ligand molar ratio of 1:2 which dissolved in 10 ml of absolute ethanol. The metal salts were added gradually drop by drop to a solution of ligand. The reaction mixture was allowed to stir magnetically for 3 hr at room temperature. The reaction mixture was filtered, washed with ethanol and dried at 50 LC by using an oven for 1 hr.[19]

Drug Design

To understand the structural basis for the activities of the inhibitors and to support the in vitro activity results, the binding models of the top active analogs was studied with lead structure using -

- online portal Swiss ADME
- online portal sanjeevni from IIT delhi for 2 D and 3 D structure and lipinski filter
- Glide 5.9 (Schrodinger, LLC, New York, NY, 2013) docking image

- The crystal structure of 2NYT (PDB entry 3BPF) was retrieved from the Protein Database Bank with a resolution of 2.9 Å.
- Keeping all these aspects in mind from literature review; a multidisciplinary approach was taken to develop novel potential drug-like lead molecules for targets like Nickel Schiff base complex.
- The following prime objectives were set for the present study.
- 2D structure and 3D structure of Ni Schiff base complex was prepared.
- Hits were docked into the binding pocket.

In order to attain the better pharmacokinetic profile, molecules were designed according to the 'Lipinski's Rule of Five (1997). Proposed pharmacophore model (Green Color: Represents hydrophobic residue; an aromatic group, Red Color: Represents an aromatic residue (monocyclic/bicyclic), Blue Color: Represents the numbers of hydrogen bond donor and acceptor atoms)

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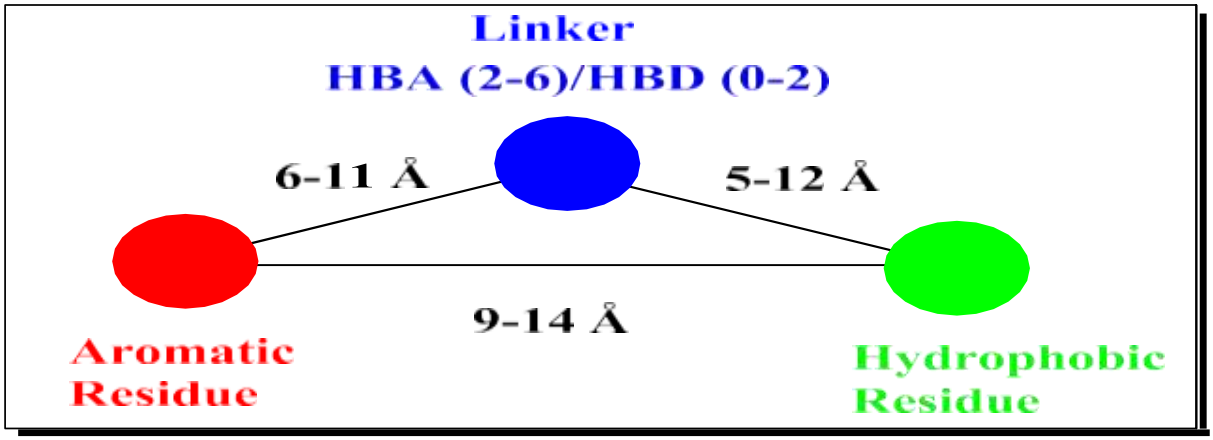

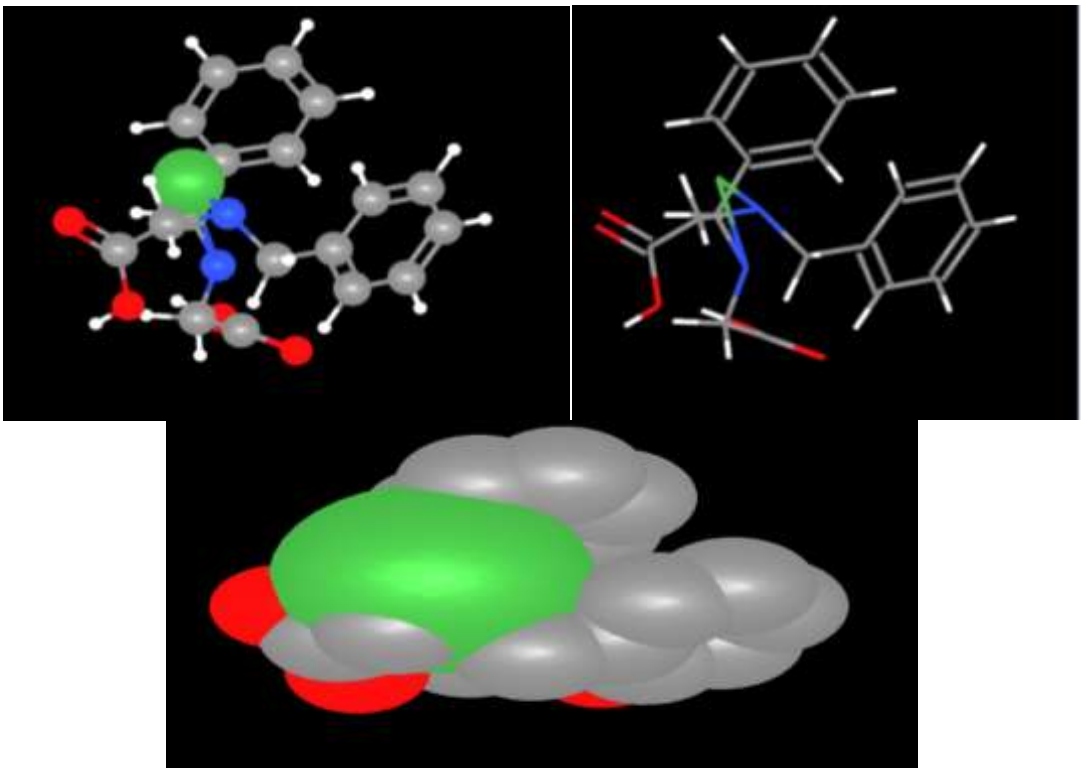

2 D and 3d Structure of Nickel – Schiff base Complex.

III. RESULT AND DISCUSSION

General

The obtained complexes were colored powders, stable for a long time in the open atmosphere. The analytical data for the ligand and its complexes together with some physical properties are summarized in Table 1. All the complexes were sparingly soluble in general organic solvents, the melting points show that all of the complexes decomposed before melting. Analytical data suggest a ratio of 1:2 for Ni(II) complex.

3.1 UV-visible

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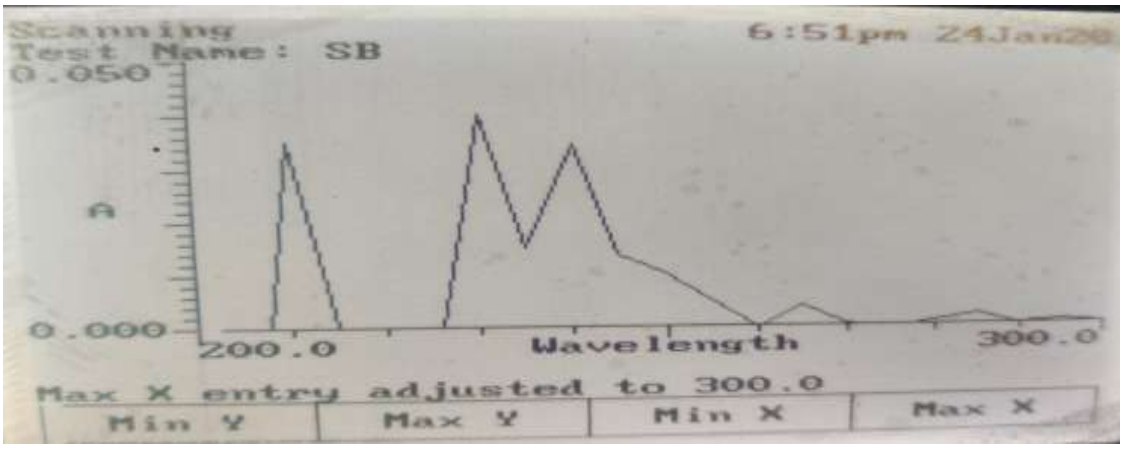
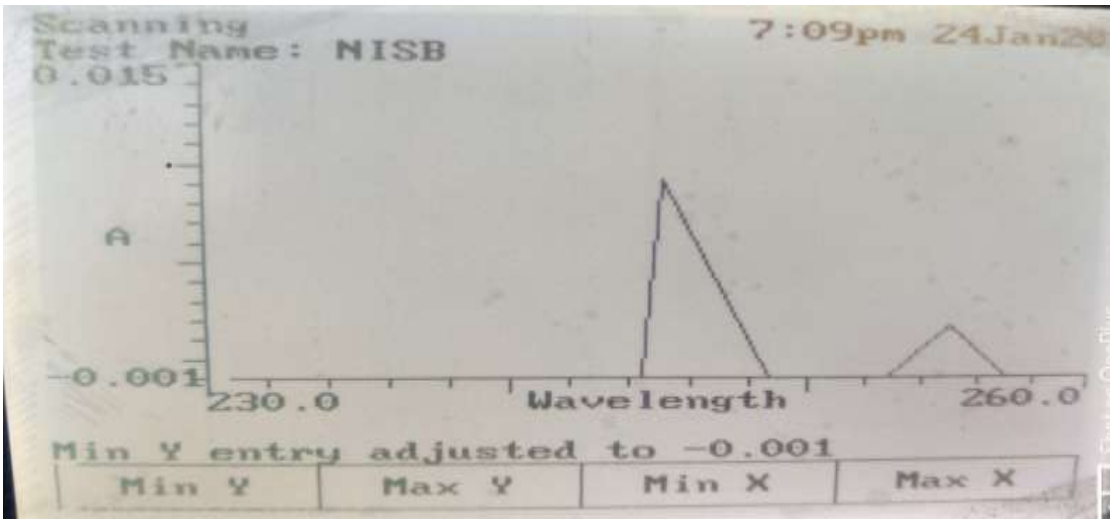
This project describes failure synthesis of Schiff bases from benzaldehyde with some amino acids, by the usual classical synthetic method. This is because of the reversible nature of synthesized Schiff bases reaction. The UV spectra of Schiff bases under study are also shown in Fig.2 and are summarized in Table (1).



UV- VISIBLE SPECTRA OF SCHIFF BASE



UV- VISIBLE SPECTRA OF NICKEL COMPLEX WITH SCHIFF BASE

Table (1) shows the nomenclature, melting point or boiling point of Schiff bases prepared, beside their IR and UV spectra.

The IR spectra of Schiff bases under study are shown in Fig.1, and illustrate the following wave-numbers:-

A broad stretching wave-numbers range between (3385.41-3424.33)cm^{-1} Which confirm OH group in the carboxyl group of Schiff bases.

1. A strong to medium intensity bands are assigned to carbonyl groups in Schiff bases. They have a stretching frequency ranged between (1633.20-1745.51) $cm^{1.}$
2. A strong to medium intensities bands are assigned to carbon nitrogen double bond i.e C = N, with stretching frequency range between (1594.01-1625.00)cm^{-1}.
3. Schiff bases (4), shows a medium absorption band a wavenumber of 738.75$cm^{-1}$for carbon sulphur C-S linkage.
4. Schiff bases numbers 2 and 4 show a linkage for sodium of carboxyl acid i.e -ONa at a wavenumbers of 645.95(s) and 759.86 (m) respectively. These values confirm the

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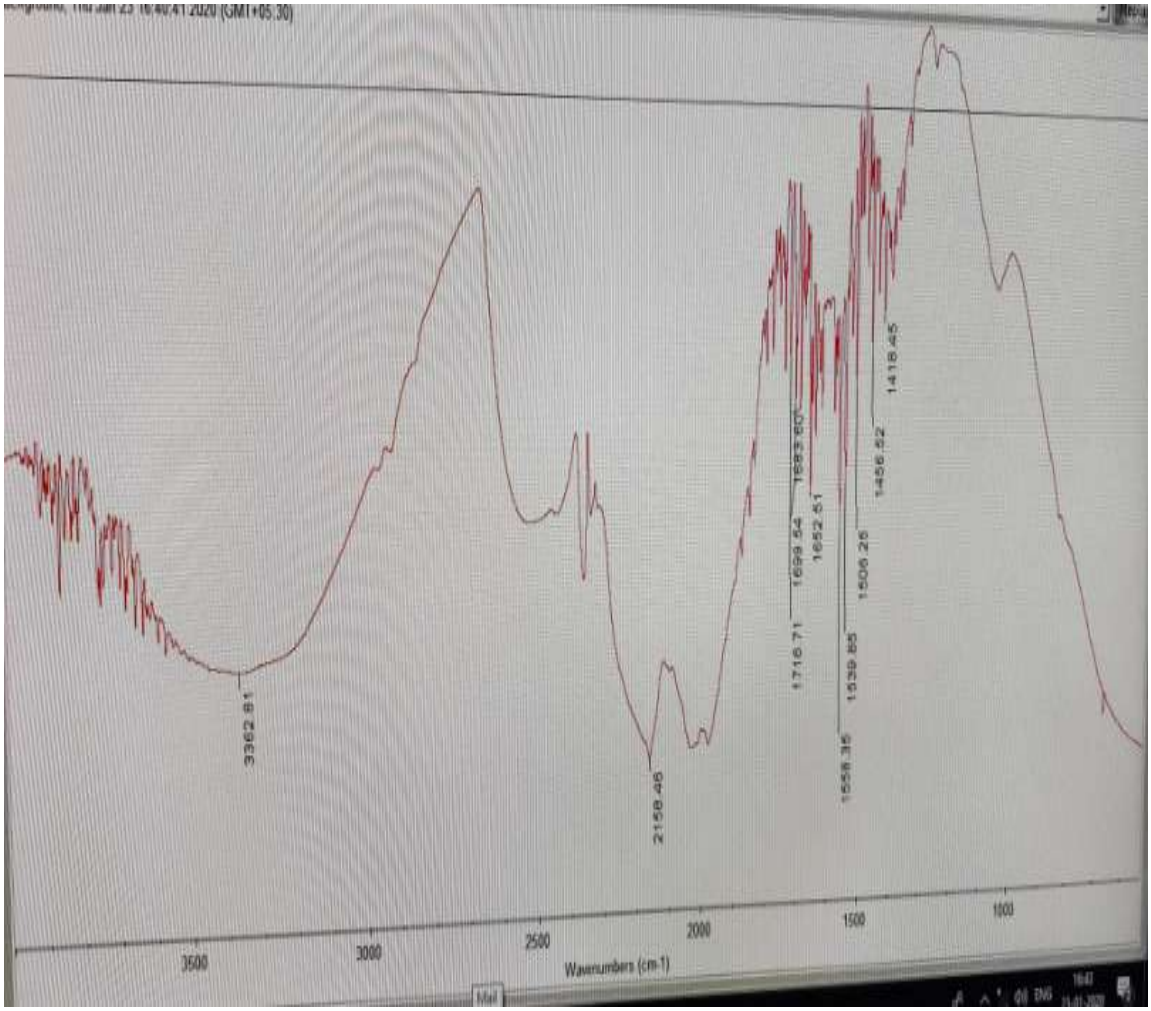
existence of these compounds as a sodium salts for carboxylic acids. These support the solubility and ignition testes stated before.

3.2. Infrared spectra

The FTIR spectra provide valuable information regarding the nature of the functional group attached to the metal atom. The infrared spectra of the ligand showed a band at 1527 cm ^{1} which was attributed to mC,N band of ring which remained unchanged in all complexes, mC,N band at 1591 cm ^{1} was observed due to the azomethine group which shows a shift to lower frequencies in all complexes almost between 10 and 30 cm ^{1} which may be indicating the involvement of –C,N nitrogen in coordination to the metal ion (Raman et al.,2007; Mitu et al., 2012).



FTIR graph for Nickel-Schiff base compund

No.	Nomenclator	m.p or B.p* (c°)	colour	IR bands cm^{-1}			
				OH	C = O	C = N	UV bands λnm(ε_{max})
1	Benzylidene Glycine (Ligand)	195C° (decomp.)	milky	3423.82 (b)	1644.75 (s)	1597.43 (s)	247(1472),282(91)

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IV. REVIEW OF LITERATURE

The design, synthesis and activity of polymodal compounds for the treatment of inflammatory bowel disease are reported. The compounds, being based on a metal-Schiff base motif, are designed to degrade during intestinal transit to release the bioactive components in the gut. The compounds have been developed sequential with the biomodel compounds combining copper or zinc with a salicylaldehyde adduct. These compounds were tested in a formalin induced colonic inflammation model in BK:A mice. From these studies a trimodal compound based on a zinc Schiff base analogue of sulfasalazine was designed. This was tested against a trinitrobenzenesulfonic acid (TNB) induced colitic model in Wistar rats. The use of two models allows us to test our compounds in both an acute and a chronic model. The trimodal compound reported is observed to provide anticolitic properties in the chronic TNB induced colitis model commensurate with that of SASP. However, the design of trimodal compound still has the capacity for further development. This the platform reported may offer a route into compounds which can markedly outperform the anti-colitic properties of SASP. **Elaine M. Conner etal.2017**

Development of new drugs is one of the solutions to fight against the existing antimicrobial resistance threat.

V. CONCLUSION

In the present research study, we synthesized new ligand by a new alternative method for synthesis of some Schiff bases from benzaldehyde with some amino acids as given. This new compound was used to prepare some new complexes of Ni(II) which are characterized by various physicochemical and spectral analyses. The antibacterial data show that the metal complexes have biological activity compared to that of parent ligand. The development includes the use of NaOH as a new catalyst during synthesis of Schiff bases mentioned. The chemical structures of Schiff bases were studied by the use of physical methods, namely melting point or boiling point, IR and UV spectra. The definition and analysis of the important descriptor parameters implied the chemical structural characteristics which influenced antibacterial activity. The results indicated that molecular polarity and negative charge distribution of compounds were important influencers on antimicrobial activity. By analysis of the descriptor parameters of these two models, some guidance was obtained on chemical structure for the design of new compounds.

In conclusion, the Schiff bases composed of derivatives and carbonyl compounds were synthesized and characterized by spectroscopic methods UV- visible & FT-IR. The compounds were prepared by Schiff base with the carbonyl compounds in equimolar amount in ethanol. The results of spectroscopic methods were used to explain the structures of the compounds and verified the predicted Schiff base structures. Besides, the compounds which were likely to exhibit inhibition activity were examined by molecular docking methods. The possibility of exhibiting inhibition activity of the Schiff bases was estimated based on similar chemical groups (phenyl ring and nitrogen atoms) included in their structure. All of the compounds exhibited low to mild binding affinities.

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